Ischemic heart disease in women: are there sex differences in pathophysiology and risk factors?: position paper from the Working Group on Coronary Pathophysiology Microcirculation of the European Society of Cardiology

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Abstract: Cardiovascular disease is the leading cause of death in women, and knowledge of the clinical consequences of atherosclerosis and cardiovascular disease in women has grown tremendously over the past 20 years. Research efforts have increased and many reports on various aspects of ischemic heart disease (IHD) in women have been published highlighting sex differences in pathophysiology, presentation and treatment of IHD. Data, however, remain limited. A description of the state of the science, with recognition of the shortcomings of current data, is necessary to guide future research and move the field forward. In this report, we identify gaps in existing literature and make recommendations for future research. Women largely share similar cardiovascular risk factors for IHD with men; however, women with suspected or confirmed IHD have less coronary atherosclerosis than men, even though they are older and have more cardiovascular risk factors than men. Coronary endothelial dysfunction and microvascular disease have been proposed as important determinants in the etiology and prognosis of IHD in women, but research is limited on whether sex differences in these mechanisms truly exist. Differences in the epidemiology of IHD between women and men remain largely unexplained, as we are still unable to explain why women are protected towards IHD until older age compared with men. Eventually, a better understanding of these processes and mechanisms may improve the prevention and the clinical management of IHD in women.

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REVIEW

Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors?

Position Paper from the Working Group on Coronary Pathophysiology and Microcirculation of the European Society of Cardiology

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Abstract Cardiovascular disease (CVD) is the leading cause of death in women, and knowledge of the clinical consequences of atherosclerosis and CVD in women has grown tremendously over the past 20 years. Research efforts have increased and many reports on various aspects of ischaemic heart disease (IHD) in women have been published highlighting sex differences in pathophysiology, presentation, and treatment of IHD. Data, however, remain limited. A description of the state of the science, with recognition of the shortcomings of current data, is necessary to guide future research and move the field forward. In this report, we identify gaps in existing literature and make recommendations for future research. Women largely share similar cardiovascular risk factors for IHD with men; however, women with suspected or confirmed IHD have less coronary atherosclerosis than men, even though they are older and have more cardiovascular risk factors than men. Coronary endothelial dysfunction and microvascular disease have been proposed as important determinants in the aetiology and prognosis of IHD in women, but research is limited on whether sex differences in these mechanisms truly exist. Differences in the epidemiology of IHD between women and men remain largely unexplained, as we are still unable to explain why women are protected towards IHD until older age compared with men. Eventually, a better understanding of these processes and mechanisms may improve the prevention and the clinical management of IHD in women.

Keywords Gender • Ischaemia • Epidemiology • Risk factors • Microcirculation

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in both women and men worldwide and a major cause of morbidity. According to the Global Burden of Disease, in 2004, CVD caused almost 32% of deaths in women worldwide vs. 27% in men.[1] In Europe, 54% of all females' death are from CVD vs. 43% in men.[2] Ischaemic heart disease (IHD), the most common form of CVD, is also the single most frequent cause of death in Western countries. In Europe, over one in five women (22%) and men (21%) die from IHD.[2] With the ageing of the population, and because of women's longer life expectancy than men, the proportion of persons, particularly women, who will die of CVD is expected to rise even further in the upcoming decades.

2. Cardiovascular mortality

In many Western countries, cardiovascular mortality has declined among women since the mid-1960s, as it has in men.[3] In the USA,

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however, the total number of deaths due to CVD has slightly increased in women up to the year 2000, whereas it has decreased among men.[4] This increase probably reflects changing population demographics towards a larger proportion of older people, the majority of whom are women. Indeed, when examining age-standardized death rates rather than death counts, a similar decline is noted in women and in men in the USA and many other Western countries.[3,5,6]

After the year 2000, both the death rates and the number of cardiovascular deaths have shown a similar, if not steeper, downward trend in American women compared with men.[4] However, when looking at different age groups, the decrease in mortality appears to have slowed down since 2000 in middle-aged women and men (age 35–54 years), whereas it has continued steadily among older people.[7] In addition to an overall decline in cardiovascular mortality from population statistics, there has been a decline in hospital mortality rates for acute myocardial infarction (AMI) among American women and men of all ages, which has been more substantial in women than in men.[8]

It should be noted that these favourable trends are not universal. For example, they do not apply to Eastern Europe, where mortality from both IHD and CVD is still rising for both women and men. Exceptions are Hungary, whose rates levelled off (at very high rates) in the mid-1990s, and Poland and the Czech Republic, whose rates have tended to decline since the mid-1990s.[3] In the Russian Federation, mortality rates from IHD and CVD for both women and men during 1995–98 were among the highest in the world.

3. Risk factors

3.1 Traditional risk factors

As shown by the INTERHEART study, a large international case–control study of AMI, risk estimates associated with traditional cardiovascular risk factors are overall similar in women and men and across various regions of the world.[9] However, the increased risk associated with hypertension and diabetes and the protective effect of exercise and alcohol appear to be somewhat larger in women than in men. Collectively, nine potentially modifiable risk factors (smoking, hypertension, diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, plasma apolipoproteins, and psychosocial factors) account for 94% of the population attributable risk of AMI in women and 90% in men.[9] For young women with favourable levels of all five major risk factors (smoking, hypertension, diabetes, serum cholesterol and body mass index), IHD and CVD are rare events.[10] Unfortunately, only about 20% of women younger than 40 years of age meet these low-risk criteria[10] and 48% of women have a clustering of three or more metabolic risk factors for IHD.[11]

3.1.1 Smoking

Smoking is the single most important preventable cause of IHD in women and the leading cause of IHD in women younger than 50 years old.[12] There is a dose-dependent relationship between total cigarettes consumption per day and risk of AMI; as few as one to five cigarettes per day increase a patient's risk.[9,13] There is also a well-established increased risk of venous thrombosis and IHD for women who both smoke and use oral contraceptives.[14] After cessation of smoking, the risk of IHD in both women and men declines rapidly (within months) and falls to the level of the risk among non-smokers within 5–10 years.[13,15] Exposure to passive smoking is also a risk factor for IHD in women, increasing their risk of 24% (22% in men).[16] Although the prevalence of smoking is still slightly higher in men than in women, the decline in tobacco use in recent decades has been less pronounced in women than in men.

3.1.2 Hypertension

For women, as for men, hypertension is a major cause of IHD, as well as of congestive heart failure and stroke.[17] Hypertension is a highly prevalent risk factor that becomes more common in women than in men over the age of 55 years and is particularly prevalent among black women.[18] In the INTERHEART study, the population attributable risk for hypertension was 36% in women, indicating that the risk of AMI could be reduced by 36% where hypertension was eliminated as a risk factor. The corresponding figure in men was 19%.[9] Hypertension is two to three times more common in women taking oral contraceptives, especially among obese and older women, than in women not taking them.

In older women, isolated systolic hypertension is the most common form of hypertension. A three-fold increase in IHD and stroke is found in women with a systolic blood pressure >185 mmHg when compared with women with a level of <135 mmHg.[19] Control of any form of hypertension has been demonstrated to reduce the risk of IHD and stroke in both sexes, as shown by large clinical trials with a fair representation of women.[20] Unfortunately, the ongoing National Health and Nutrition Examination Study (NHANES) survey has continued to show low rates of hypertension awareness, treatment, and control among American women, as in men, although these rates have increased over time.[21,22]

3.1.3 Dyslipidaemia

Almost half (48%) of American women 20 years of age or older have a total cholesterol level $\geq$ 200 mg/dL, and almost one-third (32%) have an LDL cholesterol $\geq$130 mg/dL.[4] Although women aged 20–50 years tend to have more favourable lipid profiles than men, after the onset of menopause cholesterol levels increase in women, whereas they remain steady in men. Total and LDL cholesterol levels predict fatal IHD in both middle-aged ($<$65 years) and older ($\geq$65 years) women, but the strength and consistency of these relationships in older women is diminished.[23]

Reduced HDL cholesterol and high triglyceride levels appear to be more important risk factors in women than in men. HDL cholesterol inversely predicts IHD in both middle-aged and older women, whereas it does not in older men.[23] Among 32 826 post-menopausal women from the Nurses' Health Study, HDL cholesterol was the lipid parameter that best discriminated the risk of IHD.[24] Hypertriglyceridaemia, on the other hand, is associated with 37% increased CVD risk in women, independent of other risk factors including HDL cholesterol; the corresponding estimate for men is 14%.[25]

In women with known CVD, the treatment of hyperlipidaemia is effective in reducing IHD events and IHD mortality, although it does not affect total mortality. For women without CVD (primary prevention), lipid lowering does not affect total or IHD mortality; lipid lowering may reduce non-fatal IHD events, but evidence is insufficient to determine this conclusively.[26] The recent Intervention Trial Evaluating Rosuvastatin (JUPITER) evaluated the benefits of statin therapy in apparently healthy individuals with elevated high-sensitivity C-reactive protein but without an elevation in LDL cholesterol. Among women, statin therapy significantly reduced the primary

combined endpoint of AMI, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death.[27] However, because of the small number of events, the absolute risk reduction was small (about half of a percentage point) and the reduction of 'hard' endpoints such as fatal or non-fatal AMI, stroke or cardiovascular mortality or total mortality was not statistically significant. Therefore, it is still debatable whether statins, or other lipid-lowering medications, are useful for the primary prevention of CVD in women. Given the small absolute risk of CVD in middle-aged women (those mostly targeted by primary prevention efforts), consideration of the risk/benefit ratio for any intervention is particularly important.

3.1.4 Type 2 diabetes

Diabetes mellitus is a major risk factor for IHD for both men and women, and among women, it nullifies the female protection towards developing IHD compared with men.[28] Although diabetes has often been associated with a higher IHD risk in women than in men, this is in part due to a higher rate of coexisting risk factors in women with diabetes[29] and to the better survival (relative to men) of women without diabetes.[28] The mortality rates of women with diabetes are actually similar, or less, that of men with diabetes.[28,29] These statistics, however, may be worsening. CVD mortality reductions in the past 30 years have been achieved for diabetic men but not for diabetic women; a better survival for women with diabetes than men noted in the 1970s and early 1980s was essentially eliminated in 1988–2000.[30]

3.1.5 Obesity

Obesity is an important risk factor for diabetes and CVD. It is found in 33% of women (and 31% of men), including 7% women (3% men) being extremely obese, defined as a body mass index of ≥ 40.[31] Obesity is particularly a problem among black women (54 vs. 30% in white women); the prevalence of extreme obesity is 15% in this group.[31]

There is a gradient of coronary risk with increasing overweight, with the heaviest category of women having a four-fold increased risk for CVD compared with lean women.[32] Polycystic ovary syndrome is found in 10–13% of women but is often unrecognized; it is linked with a clustering of risk factors, including obesity and type 2 diabetes mellitus, and increased IHD risk after menopause.[33] Therefore, polycystic ovary syndrome may contribute to the increased cardiovascular risk associated with obesity among women.

3.1.6 Trends in risk factors

Over the 1990s, there have been mixed trends in CVD risk factors for both women and men. On the positive side, between 1988 and 2002, both sexes experienced a reduction in the prevalence of high-risk levels of cholesterol; on the other hand, an increase in the prevalence rates of obesity and elevated C-reactive protein was noted, particularly among women.[34] Furthermore, the proportion of women with high blood pressure increased, whereas it decreased among men. A recent update from the same ongoing US survey, up to 2004, provided additional evidence of a somewhat worsening risk factor profile among women.[35]

3.2 Novel biomarkers

In an effort to improve risk prediction and guide prevention, more than 100 new risk markers have been proposed particularly for the large segment of the population who is currently classified as being at intermediate risk based on existing risk algorithms. Consensus conferences, however, have consistently recommended against the use of these markers for lack of evidence that they help improve risk prediction.[36,37] A recent summary of systematic reviews conducted for the United States Preventive Services Task Force has reviewed the evidence concerning nine novel risk factors: C-reactive protein, coronary artery calcium score as measured by electron-beam computed tomography, lipoprotein(a) level, homocysteine level, leucocyte count, fasting blood glucose, periodontal disease, ankle-brachial index, and carotid intima–media thickness.[38] Each factor's potential clinical value was evaluated by using a set of criteria that emphasized the effect on the reclassification of intermediate-risk persons. This review concluded that current evidence does not support the routine use of any of the nine risk factors for screening and risk stratification of intermediate-risk persons. Of the risk markers evaluated, C-reactive protein was the best candidate for screening; however, evidence is still lacking to recommend routine use. In women, in particular, a C-reactive protein level of >3.0 mg/L reclassified only 5% of intermediate-risk women in the Women's Health Study[39] and none in the Cardiovascular Health Study,[40] suggesting a small and inconsistent effect.[38] However, when incorporated into the Reynolds Risk Score, C-reactive protein assessment may be of utility in women, as reported in more detail in the following section, although validation of this risk algorithm is needed in different populations of women.

3.3 Risk scores for IHD

An increasing number of CVD risk factors have a cumulative effect on IHD risk both in women and in men. For example, among women aged 18–39 years without prior IHD enrolled in the Chicago Heart Association Detection Project in Industry, the age-adjusted rate of IHD per 10 000 person-years, after 31 years of follow-up, was lowest for low-risk women (0.7) and increased with increasing number of CVD risk factors to 2.4 in women with one risk factor and to 5.4 in women with two or more risk factors.[10] The INTERHEART study clearly demonstrated the cumulative effect of modifiable risk factors, including current or former smoking, diabetes, hypertension, abdominal obesity, psychosocial stressors, irregular consumption of fruits and vegetables, no alcohol intake, avoidance of regular exercise, and plasma lipids.[9]

Probably, the best-known risk algorithm for IHD for asymptomatic persons is the Framingham Risk Score (FRS), which includes age, hypertension, smoking, diabetes, and hyperlipidaemia.[41] A problem with this score is that much of the middle-aged population is classified as low to intermediate risk. This is particularly true for women: even up to age 80 years, more than three quarters of women have a 10-year Framingham risk of $<10\%$.[42] Many other risk scores have been proposed that have mostly included the same traditional risk factors, but have occasionally added other factors such as family history, measures of social deprivation, or new biomarkers such as C-reactive protein. Some of the scoring systems developed in European countries include the SCORE (Systematic Coronary Risk Evaluation), the ASSIGN (Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network/SIGN to Assign Preventative Treatment), and the QRISK (QRESEARCH cardiovascular risk algorithm).[43] Whether these risk scores perform better than the FRS for risk prediction in women remains to be demonstrated.

A risk score that has been developed specifically for women is the Reynolds Risk Score,[44] whose main difference from the FRS is the

incorporation of parental history of IHD and C-reactive protein. This score reclassified 15% of intermediate-risk women to high risk in the Women's Health Study; therefore, it has promise. However, it needs validation in other populations.

3.4 Psychosocial risk factors

There is growing evidence that psychological stress can influence the onset and clinical course of IHD,[45] and this may be especially true for women. In the INTERHEART study, the combined exposure to psychosocial risk factors including depression, perceived stress at home or work, low locus of control, and major life events was significantly associated with AMI with an adjusted odds ratio (OR) of 2.6 in men and 3.5 in women.[9] Individually, each of these factors predicted AMI in a fairly similar fashion in both men and women.[46]

3.4.1 Depression

Depression is about two-fold more prevalent in women than in men; it is especially common, up to 40%, in younger women with AMI.[47] Depression is an important risk factor for adverse cardiac events in women, increasing a woman's risk of at least 50%.[48–50] In addition to cardiac outcomes, depression is related to worse quality of life in cardiac patients[51] and worse health status benefits after bypass surgery, particularly in women.[52] Furthermore, depression is one of the strongest predictors of non-adherence to medical treatment[53,54] and an important correlate of lifestyle behaviours such as smoking[55] and sedentary lifestyle.[56]

3.4.2 Chronic emotional distress

Factors such as anxiety, marital stress, and exposure to early life adversities have been linked to cardiovascular risk in women. On the basis of a recent meta-analysis, anxiety is a moderate but independent risk factor for incident IHD and cardiac death in both men and women, although individual study results are heterogeneous.[57] A series of studies of Scandinavian women with acute coronary syndromes have demonstrated robust associations of marital stress with subsequent cardiac events,[58] as well as with progression of coronary artery disease measured with quantitative coronary angiography.[59] A study of US women also linked marital satisfaction to less atherosclerosis in the carotid arteries and aorta measured by ultrasound and to less rapid progression of carotid atherosclerosis.[60] Psychological trauma, particularly if occurring early in life, such as childhood maltreatment, is an emerging risk factor for IHD which is particularly common among women.[61] Early trauma is also a risk factor for depression,[62] which may contribute to IHD risk in women exposed to childhood trauma.

3.4.3 Acute stress

Acute psychological factors such as stressful events, acute anger, sudden mood disturbances, and extreme excitement can trigger AMI and sudden cardiac death in susceptible individuals.[63] Although it is unknown whether there are sex differences in these effects, a stress-induced condition known as 'takotsubo cardiomyopathy' is almost exclusively seen among women.[64] It manifests as severe, reversible left ventricular dysfunction, with markedly elevated levels of plasma catecholamines.

3.4.4 Psychological interventions

Unfortunately, psychological interventions aimed at reducing stress or treating depression or other psychosocial risk factors have shown little to no effect on IHD incidence and total or cardiac mortality, although they do achieve small reductions in anxiety and depression in patients with IHD.[65] When results are reported separately by sex, men show a borderline statistically significant benefit [OR 0.73, 95% confidence interval (CI) 0.51–1.05], whereas in women, the estimate is null (OR 1.01, 95% CI 0.46–2.23).[66] It may be that traditional psychosocial interventions do not work well for women and that strategies that address more specifically women's needs and stressors should be developed. This is suggested by a recent study by Orth-Gomer *et al.*,[67] documenting a remarkable decrease in mortality (about 70% lower) in women with IHD randomized to a stress-reduction intervention specifically tailored to women, compared with usual care. Although promising, the efficacy of such intervention needs to be confirmed in other studies.

4. Pathophysiology

4.1 Atheroma burden and morphology

Women have less obstructive coronary artery disease than men along the entire spectrum of acute coronary syndromes[68–70] and across all age groups.[70] This advantage appears more marked in the coronary tree than in other vascular beds. The population-based Rotterdam Study examined sex differences in atherosclerosis at different sites in the vascular tree among participants of age $\geq$55 years.[71] A high calcium score ($>$1000) was found more frequently in men than in women in all age categories; interestingly, sex differences were more evident in the coronary arteries than in other vascular territories. Nicholls *et al.*[72] reported a lower atheroma volume in women with angiographic coronary artery disease than in men, including both intraluminal plaque and atheroma within the media, despite the presence of more cardiovascular risk factors in women. Recently, Han *et al.*,[73] by measuring atheroma burden using intravascular ultrasonography, have extended this observation to patients without obstructive coronary artery disease and demonstrated that even at this early stage, women have a lower atheroma burden and different atheroma morphology compared with men.

4.2 Vascular function

Community samples have demonstrated that women have better peripheral endothelial function than men (measured as per cent of flow-mediated vasodilation from baseline) until about age 70 and at all levels of risk factors.[74–76] Better vascular function has also been noted in women referred for coronary angiography but without obstructive coronary artery disease, compared with men. In the study by Han *et al.*,[73] in addition to less plaque burden, women had less diffuse epicardial endothelial dysfunction than men. Whether better vascular function in women than men is also found among patients with AMI or other acute coronary syndromes is not known. However, abnormal endothelial function appears to be a prognostic factor in women, as suggested by a small follow-up study part of the Women's Ischaemia Syndrome Evaluation (WISE) study.[77] More data are needed, however, to confirm these findings.

4.3 Vascular tissue repair

Ultimately, the balance between injury and repair is thought to be the major determinant of CVD progression, with endothelial progenitor cells (EPCs) playing an important role in vascular repair. Endogenous mobilization of EPCs is associated with an enhanced

re-endothelialization, an improvement of endothelial function, and a reduced atherosclerotic burden. Thus, EPCs may provide a circulating pool of cells that could constitute a cellular 'repair' mechanism at the sites of vascular injury. A recent study based on 210 healthy subjects (104 males and 106 females) demonstrated higher steady-state levels of EPC (CD34+KDR+) in fertile women than in men, whereas they were not different between post-menopausal women and age-matched men.[78] These sex gradients mirrored differences in cardiovascular profile, vascular function (brachial artery flow-mediated dilation), and carotid intima–media thickness. EPCs are mobilized cyclically in fertile women according to the menstrual cycle,[78,79] in synchrony with the level of circulating 17β-oestradiol,[79] and they could represent an important mechanism of protection for premenopausal women. Therefore, oestrogen may play a role in stimulating vascular repair; data from animal studies support this notion.[80]

4.4 Microvascular disease

Coronary microvascular dysfunction is a term used to designate abnormalities in the vasomotor or metabolic regulation of the small coronary arterioles (<500 μm in diameter), which are not visualized by coronary angiography and are the main determinants of coronary vascular resistance.[81] It is a complex phenomenon that includes both endothelium-dependent and -independent pathways but can also be caused by structural changes in the vessel wall, such as vascular remodelling. Coronary microvascular disease may precede the development of frank IHD and bears independent prognostic significance.[82] Coronary microcirculatory function can be assessed invasively by measuring coronary flow reserve in response to adenosine with an intracoronary Doppler wire. Non-invasive methods for the measurement of coronary flow reserve include positron emission tomography, magnetic resonance imaging, and transthoracic echocardiography with contrast material.[81]

According to experimental studies, sex plays a relevant role in a number of microvascular mechanisms which may affect microvascular function and disease. Sex-specific differences in microvascular blood flow and vasodilatory capacity are observed very early in development. In a study on skin microcirculation in newborn preterm (24–28 weeks) infants, Stark *et al.*[83] observed that male infants had higher baseline flow than females. In animal experiments, differences in superoxide concentration and vascular permeability of venules were also described.[84] Some of the reported sex differences are related to gonadal hormones and their receptors. However, genetic differences may also exert effects independent from gonadal function.[85]

On the basis of experimental data and clinical observation, coronary microvascular dysfunction is put forth as a major aetiological factor for IHD in women and a frequent determinant of chest pain in the absence of significant coronary obstruction—known as syndrome X or 'microvascular angina'.[86,87] To date, however, microvascular angina remains a controversial entity,[88] and few clinical studies have addressed the role of microvascular dysfunction as a determinant of IHD in women other than within the context of cardiac syndrome X. In a recent follow-up study of 189 WISE women with suspected coronary ischaemia, coronary flow reserve after intracoronary adenosine was significantly related to increased risk of major adverse outcomes (death or hospitalization for non-fatal AMI, congestive heart failure or stroke), with an adjusted hazards ratio of 1.14 per unit decrease in log-transformed coronary flow reserve.[89] Data are needed in less selected samples of women, and using non-invasive methods of coronary flow reserve, to confirm these findings. Also, data are needed to support the concept that this phenomenon is more prevalent among women than men. Currently, the only proof is the observation that cardiac syndrome X is more frequent in women than in men, but this syndrome only accounts for a small proportion of IHD in women. The few studies that have compared coronary flow reserve in response to adenosine between women and men referred for coronary angiography have found similar values.[73,90] In one study, coronary flow reserve was lower in women, but the difference was largely explained by women's older age and smaller body size.[73]

4.5 Autonomic function

There are important sex differences in the autonomic nervous control of the cardiovascular system. Men tend to have a higher sympathetic cardiac autonomic activity, whereas women tend to have a higher parasympathetic activity.[91] These differences may be the result of developmental differences (e.g. body fat distribution) or hormonal differences between women and men.[91,92] Other factors that modulate or alter autonomic cardiac activity, and may potentially influence sex differences, include age,[93] obesity,[92] changes in hormone levels,[91] inflammation,[94] and psychological disorders (e.g. depression).[95]

Airaksinen *et al.*[96] showed that vagal activation was more common in women than men during acute coronary occlusion, suggesting that this might have beneficial antiarrhythmic effects. However, in patients with cardiac syndrome X, who are mostly post-menopausal women, an imbalance of autonomic nervous activity has been reported. Lanza *et al.*[97] showed I-metaiodobenzylguanidine myocardial scintigraphy defects, a measure of autonomic nervous system activity, in 75% of cardiac syndrome X patients (64% women). In addition, in patients with cardiac syndrome X, a relationship between vagal impairment, measured by means of heart rate variability, and non-invasive coronary flow reserve measurements has been described.[98] Furthermore, Ponikowski *et al.*[99] showed that marked vagal withdrawal, detected by heart rate variability analysis, preceded ST-segment depression on 24 h Holter monitoring in a predominantly female sample (19 women out of 23 patients). Although it is known that women are more often affected by cardiac syndrome X than men, no study so far has been conducted to examine sex differences in cardiac autonomic activity in a broad range of IHD patients.

Another condition in which autonomic dysfunction is likely to play a pathogenic role is takotsubo cardiomyopathy. A recent study showed significant impairment in heart rate variability at the index event compared with after 3 months,[100] suggesting that acute autonomic dysfunction may induce neurogenic stunning of the myocardium leading to the clinical picture of stress-induced cardiomyopathy. Therefore, although women have normally a more favourable autonomic function profile than men, specific syndromes that are more common among women (cardiac syndrome X and takotsubo cardiomyopathy) are paradoxically linked to adverse autonomic function.

4.6 Role of sex hormones

The lower incidence of CVD in premenopausal women compared with men of similar age and the menopause-associated increase in CVD have long suggested that ovarian hormones underlie a protective effect on the cardiovascular system for women. Indeed, sex steroid hormones exert multiple direct and indirect effects on cardiovascular physiology.[101] Up to now, research has focused on the effects of oestrogen and oestrogen receptors (ERs), whereas other

hormones, such as progesterone and testosterone and their receptors (PR and AR), have received much less consideration.

4.6.1 Cardiovascular effects of oestrogens

Oestrogens improve the arterial wall response to injury and inhibit the development of atherosclerosis by promoting re-endothelialization, inhibiting smooth muscle cell proliferation, and matrix deposition following vascular injury.[102] Oestrogens also decrease systemic vascular resistance, improve coronary and peripheral endothelial function, and prevent coronary artery spasm in women with and without coronary atherosclerosis.[103,104] Interestingly, intracoronary infusion of oestradiol improves endothelial function and coronary blood flow in female patients, but not in male patients with coronary artery disease.[104]

Oestrogens cause vasodilation through both rapid increases in the production of nitric oxide (NO) and the induction of NO genes.[102] Oestrogens also modulate relaxation through the endothelium-derived hyperpolarizing factor,[105] by inducing vasodilator prostanoids (PGE_2 and PGI_2)[106] and by inhibiting the production of endothelin-1.[107] Additionally, oestrogens modulate myogenic vascular responses by reducing the basal tone of microvessels.[106] The majority of these effects have been attributed to oestrogens acting on two distinct receptors, ERα and ERβ, which are expressed both in vascular endothelial and smooth muscle cells.[102] ERα appears to mediate most of the protective effects of oestrogen against vascular injury and atherosclerosis.[108] ERβ expression is enhanced in the vascular wall of women with IHD, whereas ERα predominates in unaffected women.[109]

Most of the data on the cardiovascular effects of oestrogens relate to vascular function. Much less is known about oestrogens effects on the myocardium. ERβ is present in myocardial cells, where it regulates the expression of NO synthases.[110] Additionally, oestrogens affect signalling of genes involved in cardiac conduction, such as I_{sk} and HK2 (cardiac potassium channels) and connexion 43.[110] In female mice, for example, oestrogens have been shown to prolong AV nodal conduction and the right ventricular effective refractory period.[111]

In addition to oestrogens, progesterone may also contribute to sex-specific differences in the regulation of vascular function; its effects, however, remain controversial.[112] Testosterone, on the other hand, was shown to have adverse effects on blood pressure and cardiovascular morbidity and mortality.[113]

4.6.2 Post-menopausal hormone therapy

Given the many potentially beneficial effects of oestrogens on cardiovascular physiology, much expectation was placed on the protective effects of post-menopausal hormone therapy for CVD prevention in women. Initial observational studies did show a reduced incidence of CVD in post-menopausal women using hormone therapy compared with non-users.[114,115] However, it has recently become clear that hormone therapy has complex biological effects, e.g. it has both anti-inflammatory and proinflammatory effects and it both activates coagulation and improves fibrinolysis.[116] Effects depend on many factors, including route of administration, doses of oestrogens, and age of the women, among others. Given orally, hormone therapy clearly increases C-reactive protein.[117]

The Heart and Estrogen/Progestin Replacement Study (HERS), and the Women's Health Initiative (WHI) clinical trials did not support beneficial effects of hormone therapy in post-menopausal women, neither in secondary nor in primary cardiovascular prevention.[118–120] In fact, the WHI study was terminated early due to a small but significant increase in cardiovascular events and other adverse outcomes in the hormone therapy group. In trying to explain these unexpected results, it has been argued that the timing of initiation of hormone therapy after the onset of menopause may influence the response to treatment for CVD prevention. *Post hoc* analyses of the WHI trial suggested that the CVD risk may be decreased when oestrogen-only therapy is started earlier, within 10 years of menopause, but results were not statistically significant.[121] For the combination of oestrogen and progestin therapy, there was no indication of a decreased CVD even among women who initiated therapy within 10 years after menopause; a possible cardioprotective effect in these women became apparent only after 6 years of use.[122] Because the typical duration of hormone therapy is <10 years, most women considering combined oestrogen plus progestin therapy for the relief of menopausal symptoms should not expect protection against CVD. Thus, no trial of hormone therapy has conclusively demonstrated a beneficial effect towards CVD in either primary or secondary prevention; if anything, risk is slightly increased. Therefore, hormone therapy should not be used for the prevention of CVD in women.

5. Conclusions and recommendations for future research

Women largely share similar cardiovascular risk factors for IHD with men; however, there are important sex differences in the prevalence of coronary atherosclerosis and coronary vascular physiology with relevance to IHD risk. Experimental data suggest complex differences in the regulation of vasomotor function of microvessels of females and males. These experimental findings contribute to the understanding of sex differences in IHD. A larger role has been proposed for coronary endothelial dysfunction and microvascular disease in the aetiology and prognosis of IHD in women than in men, but research is limited. Key questions remain about the prevalence of these vascular abnormalities in women with and without symptomatic IHD and whether they affect women more than men. More data are also needed to explain why women are protected towards IHD until older age. Differences in epidemiology may reflect important aspects of cardiovascular pathophysiology that differ between the sexes. Eventually, a better understanding of these processes may improve the clinical management of IHD in women, because it may help to devise new strategies for the prevention, detection, and treatment of IHD that are better tailored to women.

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